REMARKS

Applicant intends this response to be a complete response to the Examiner's Non-Final Office Action. Applicant has labeled the paragraphs in his response to correspond to the paragraph labeling in the Office Action for the convenience of the Examiner.

DETAILED ACTION

Specification

The Examiner contends as follows:

1. The use of the trademarks AMERICAN TYPE CULTURE COLLECTION, ATCC, SEPHADEX, SEQUENASE, and HOECHST have been noted in this application. They should be capitalized wherever they appear and be accompanied by their respective generic terminology.
2. Although the use of trademarks is permissible in patent applications, the proprietary nature of the marks should be respected and every effort made to prevent their use in any manner which might adversely affect their validity as trademarks.
3. The disclosure is objected to because of the following informalities: On 03 April 2005 an amendment to the specification was made. Upon review of page 5 of the amendment, it is noted that "ethanol" is listed twice. See line 17 and the last line of page 5.
4. Appropriate correction is required.
5. The specification is objected to as documents have been improperly incorporated by reference. It is noted that the specification contains reference to numerous documents, yet the complete bibliographical citation has not been provided. In general, only the last name of the first named author and publication year are provided. A review of the original specification fails to find where any bibliographical index has been provided. As a consequence, it is not readily apparent as to just which journal(s) the publications appeared in, much less identify where in the various articles the essential materials is to be found. As set forth in Advanced Display Systems Inc. v. Kent State University (Fed. Cir. 2000) 54 USPQ2d at 1679:

   Incorporation by reference provides a method for integrating material from various documents into a host document--a patent or printed publication in an anticipation determination--by citing such material in a manner that makes it clear that the material is effectively part of the host document as if it were explicitly contained therein. See General Elec. Co. v. Brenner, 407 F.2d 1258, 1261-62, 159 USPQ 335, 337 (D.C. Cir. 1968); In re Lund, 376 F.2d 982, 989, 153 USPQ 625, 631 (CCPA 1967). To incorporate material by reference, the host document must identify with detailed particularity what specific material it incorporates and clearly indicate where that material is found in the various documents. See In re Seversky, 474 F.2d 671, 674, 177 USPQ 144, 146 (CCPA 1973) (providing that incorporation by reference requires a statement "clearly identifying the subject matter which is incorporated and where it is to be found"); In re Saunders, 444 F.2d 599, 602-02, 170 USPQ 213, 216-17 (CPA 1971) (reasoning that a rejection or anticipation is appropriate only if one reference "expressly incorporates a particular part" of another reference); National Latex Prods. Co. v. Sun Rubber Co., 274 F.2d 224, 230, 123 USPQ 279, 283 (6'h Cir. 1959) (requiring a specific reference to material in an earlier application in order to have that material considered a part of a later application); cf. Lund, 376 F.2d at 989, 13 USPQ at 631 (holding that a one sentence reference to an abandoned application is not sufficient to incorporate from the abandoned application into a new application). (Emphasis added.)
6. Accordingly, the cited documents are not considered to have been incorporated by reference and as such, have not been considered with any effect towards their fulfilling, either in part or in whole, the enablement, written description, or best mode requirements of 35 USC 112, first paragraph.

Applicants have amended the specification to correct these problems and ask for withdrawal of same.

Claim Rejections - 35 USC § 112

8. **Claims 19, 56, 70, 78, 88, and 99** stand rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention.

New Matter.

The Examiner contends as follows:

> 9. **Claims 19, 56, 70, 78, 88, and 99** all refer to a collection of amino acid positions of SEQ ID NO. 11. Claim 19 is exemplary, and for convenience, is reproduced below.
> 10. A review of the application finds that the application was originally filed with a Sequence Listing that contained 48 sequence listings, and had the following for SEQ ID NO. 11:
> 11. A review of the current Sequence Listing finds that SEQ ID NO. 11 is not some 832 amino acids in length. Further, a review of the original Sequence Listing fails to find where applicant had disclosed under any SEQ ID NO. a protein that was 832 amino acids in length.
> 12. A review of the file history fails to find where applicant contemplated, and properly incorporated by reference, the now disclosed amino acid sequence.
> 13. It is further noted that upon review of the disclosure, applicant had contemplated various mutants of Taq polymerase, and at no time was this specific amino acid sequence disclosed. In view of the apparent addition of this sequence to the disclosure, the specification and claims 19, 56, 70, 78, 88, and 99 are deemed to comprise new matter.

Applicants still strongly disagree with the Examiner. One of your own colleges considered that the specification included sufficient reference specificity to permit the inclusion of the complete sequence listing for *Taq* Polymerase I.

Moreover, any one of ordinary skill in the art would be able to identify the substitution sites indicated in specification with the correct site on the *Taq* polymerase regardless of whether the complete sequence is set forth, because the subsequences are so unique as to only occurs once in the *Taq* polymerase. Because a specification is written to an ordinary artisan, the ordinary artisan, as exemplified by one of your own colleges, would clearly know the amino acid sequence of *Taq*, a very ubiquitously used polymerase, and would be able to recognize the exact substitution sites indicated in the specification, even without the full sequence of *Taq*.

Furthermore, Applicants referenced the ATCC database for the *Taq* Polymerase I encoding sequence. Thus, an ordinary artisan would know the polypeptide sequence from the encoding nucleotide sequence listed the ATCC database for *Taq* Polymerase I.

Thus, no new matter has been added by the inclusion of the entire sequence of *Taq* Polymerase I.

However, Applicants have amended the claims at issue to include only the specific amino acid sites of *Taq* Polymerase I, an identification that would be fully understood by ordinary artisans.

Additionally, figures 3a and 3b show a representation of the crystal structure of taq polymerase that was solved by Li *et al.* 1998. '3ktq' refers to the protein sequence that was used to produce the protein crystals, and an ordinary artisan recognizes this structure/sequence association.

Response to Argument

The Examiner contends as follows:

14. At page 13 of the response received 10 March 2008, applicant's representative asserts: Applicants respectfully disagree with the Examiner. Examiner Smith required Applicants to add the fully Taq Polymerase I listing very early in the prosecution of this case, SEQ. ID NO. 11. So the sequencing listing to Taq sites are fully enabled. The Taq polymerase I sequence was contained in a document incorporated by reference: Eom et al, 1996; Li et al, 1998a; Li et al, 1998b. The sequence was added on 03-11-2004 in the sequence listing filed that day. Applicants, therefore, respectfully request withdrawal of this section 112, first paragraph rejection.

15. The above argument has been fully considered and has not been found persuasive. While agreement is reached in that, the specification was amended so to overcome a prior rejection or issue of enablement, such does not super cede the requirement that the subject matter be properly incorporated by reference. As reproduced above, applicant asserts that the information was found in documents incorporated by reference. However, there is no full bibliographic citation for the identified documents. It is also noted that applicant has not identified just where this citation was made in the original specification. As set forth in Advanced Display Systems Inc. v. Kent State University (Fed. Cir. 2000) 54 USPQ2d at 1679:

> Incorporation by reference provides a method for integrating material from various documents into a host document--a patent or printed publication in an anticipation determination--by citing such material in a manner that makes it clear that the material is effectively part of the host document as if it were explicitly contained therein. See General Elec. Co. v. Brenner, 407 F.2d 1258, 1261-62, 159 USQP 335, 337 (D.C. Cir. 1968); In re Lund, 376 F.2d 982, 989, 153 USPQ 625, 631 (CCPA 1967). To incorporate material by reference, the host document must identify with detailed particularity what specific material it incorporates and clearly indicate where that material is found in the various documents. See In re Seversky, 474 F.2d 671, 674, 177 USPQ 144, 146 (CCPA 1973) (providing that incorporation by reference requires a statement "clearly identifying the subject matter which is incorporated and where it is to be found"); In re Saunders, 444 F.2d 599, 602-02, 170 USPQ 213, 216-17 (CPA 1971) (reasoning that a rejection or anticipation is appropriate only if one reference "expressly incorporates a particular part" of another reference); National Latex Prods. Co. v. Sun Rubber Co., 274 F.2d 224, 230, 123 USPQ 279, 283 (6'h Cir. 1959) (requiring a specific reference to material in an earlier application in order to have that material considered a part of a later application); cf. Lund, 376 F.2d at 989, 13 USPQ at 631 (holding that a one sentence reference to an abandoned application is not sufficient to incorporate from the abandoned application into a new application). (Emphasis added.)

In the instant case, the specification does not identify the various documents much less identify with any degree of particularity just what is being incorporated by reference from the various documents. Accordingly, applicant cannot now rely upon these documents to overcome the deficiencies of the disclosure.

16. For the above reasons, and in the absence of convincing evidence to the contrary, the rejection is maintained.

Applicants recognize that the Examiner is reversing the previous holding of Examiner Smith,

but Applicants still contend that the incorporation of the full sequence of *Taq* Polymerase I is not new matter and secondly is not really needed as any ordinary artisan knows this sequence or can determine the position on the *Taq* Polymerase I sequence based on the partial sequences given in the specification.

Moreover, Examiner Smith new exactly what the short hand notations for the articles cited in the specification that include the *Taq* Polymerase I sequence as they are notorious in the art and are known by ordinary artisans.

18. **Claims 52, 66, 73, 83, and 94** are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

The Examiner contends as follows:

> 19. Claims 52, 66, 73, 83, and 94 have been found to contain the trademark SEQUENASE. It is noted that products represented by a trademark are subject to change without public notice. This rejection can be overcome by writing the trademark in capital letters and including, within parenthesis, a generic description of the product identified.

Applicants have amended the claims to indicate that SEQUENASE is a trademark name of a polymerase. Applicants, therefore, respectfully request withdrawal of this rejection.

Claim Rejections - 35 USC § 102/103(a)

24. **Claims 10, 13, 17, and 18** stand rejected under 35 U.S.C. 102(e) as anticipated by or, in the alternative, under 35 U.S.C. 103(a) as obvious over US Patent 6,982,146 B1 (Schneider et al.).

The Examiner contends as follows:

> 25. It is noted that while Schneider et al., was published 03 January 2006, it claims benefit of priority to provisional application 60/151,580, filed 30 August 1999. In comparison, the instant application claims benefit of priority to provisional application filed 07 July 2000. Accordingly, Schneider et al., qualifies as 102(e)-type art.
> 26. Schneider et al., disclose methods, and related compositions, for conducting sequencing reactions. As seen at column 5, the polymerase and nucleotides are both labeled, and that either can serve as a donor or acceptor of a signal, which can be fluorophores.
> 27. Schneider et al., column 9, teach explicitly of the application of fluorescence resonance energy transfer (FRET).
> 28. Schneider et al., column 10, teach, "[o]ne of ordinary skill in the art can easily determine...which fluorophores will make suitable donor-acceptor FRET pairs."
> 29. Schneider et al., column 13, disclose a plethora of polymerizing agents.
> 30. Schneider et al., column 25, teach that the fluorophore can be linked directly or indirectly to the nucleotide.
> 31. Schneider et al., column 9, teach that the donor and acceptor fluorophores need to be within 10 to 100 Angstroms of one another for fluorescence resonance energy transfer to take place.
> 32. Schneider et al., column 24, first full paragraph, teach that the linkage which couples the

fluorophore to the nucleotide can be designed such that it is cleaved, thereby releasing the fluorophore, prior to the incorporation of the next nucleotide.

33. In view of the above remarks, and in the absence of convincing evidence to the contrary, claims 10, 13, 17, and 18 are rejected under 35 U.S.C. 102(e) as anticipated by or, in the alternative, under 35 U.S.C. 103(a) as obvious over US Patent 6,982,146 B1 (Schneider et al.).

Schneider et al. do not disclose, teach or even suggest nucleotides tagged on a part of the nucleotide that is released due to action of the polymerase. All of tags disclosed by Schneider et al. are attached to either the base, sugar or backbone (alpha) phosphate. No reading of Schneider et al. permits an understanding that the tags are released by action of the enzyme alone.

Nucleotides: The major nucleotides of DNA are deoxyadenosine 5'-triphosphate (dATP or A), deoxyguanosine 5'-triphosphate (dGTP or G), deoxycytidine 5'-triphosphate (dCTP or C) and deoxythymidine 5'-triphosphate (dTTP or T). The major nucleotides of RNA are adenosine 5'-triphosphate (ATP or A), guanosine 5'-triphosphate (GTP or G), cytidine 5'-triphosphate (CTP or C) and uridine 5'-triphosphate (UTP or U). The nucleotides disclosed herein also include nucleotides containing modified bases, modified sugar moieties and modified phosphate backbones, for example as described in U.S. Pat. No. 5,866,336 to Nazarenko et al. (herein incorporated by reference).

Examples of modified base moieties which can be used to modify nucleotides at any position on its structure include, but are not limited to: 5-fluorouracil, 5-bromouracil, 5-chlorouracil, 5-iodouracil, hypoxanthine, xanthine, acetylcytosine, 5-(carboxyhydroxylmethyl) uracil, 5-carboxymethylaminomethyl-2-thiouridine, 5-carboxymethylaminomethyluracil, dihydrouracil, beta-D-galactosylqueosine, inosine, N.about.6-sopentenyladenine, 1-methylguanine, 1-methylinosine, 2,2-dimethylguanine, 2-methyladenine, 2-methylguanine, 3-methylcytosine, 5-methylcytosine, N6-adenine, 7-methylguanine, 5-methylaminomethyluracil, methoxyaminomethyl-2-thiouracil, beta-D-mannosylqueosine, 5'-methoxycarboxymethyluracil, 5-methoxyuracil, 2-methylthio-N-6-isopentenyladenine, uracil-5-oxyacetic acid, pseudouracil, queosine, 2-thiocytosine, 5-methyl-2-thiouracil, 2-thiouracil, 4-thiouracil, 5-methyluracil, uracil-5-oxyacetic acid methylester, uracil-S-oxyacetic acid, 5-methyl-2-thiouracil, 3-(3-amino-3-N-2-carboxypropyl) uracil, and 2,6-diaminopurine.

Examples of modified sugar moieties which may be used to modify nucleotides at any position on its structure include, but are not limited to: arabinose, 2-fluoroarabinose, xylose, and hexose, or a modified component of the phosphate backbone, such as phosphorothioate, a phosphorodithioate, a phosphoramidothioate, a phosphoramidate, a phosphordiamidate, a methylphosphonate, an alkyl phosphotriester, or a formacetal or analog thereof.

Such modifications however, allow for incorporation of the nucleotide into a growing nucleic acid chain. That is, they do not result in the termination of nucleic acid synthesis.

Schneider et al. at Col. 12, ll. 13-55.

EXAMPLE 3

Preparation of Fluorescent Nucleotides

This example describes how to prepare nucleotides containing at least one fluorophore, for example an acceptor fluorophore. In addition, this example lists sources of commercially available fluorescent nucleotides that can be used in the present disclosure. When choosing acceptor fluorophores, it is important that the frequency used to excite the donor fluorophore on the polymerase (Example 1) not overlap the excitation spectra of the acceptor fluorophores on the nucleotides. Each nucleotide should possess at least one acceptor fluorophore having an excitation spectrum which overlaps the emission spectrum of the donor fluorophore attached to the polymerase (Example 1), such that the emission from the donor fluorophore excites the acceptor fluorophore.

NEN Life Science Products (Boston, Mass.) offers all four deoxynucleotides and ribonucleotide analogs with fluorophores attached. There are several different fluorophores available including fluorescein, Texas Red.RTM., tetramethylrhodamine, coumarin, napthofluorescein, cyanine-3, cyanine-5, and Lissamine.TM.. In addition, Molecular Probes (Eugene, Oreg.) sells